the last time point for which plasma concentrations could be measured divided by the administered dose (in kg*h/L); t1/2: terminal half-life (in h); F: oral bioavailability: AUCnorm after intragastral administration divided by AUCnorm after intravenous administration (in %).

TABLE 8

Results of in vivo pharmacokinetic test

Example	CLblood dog [L/h/kg]
3	2.39
31	0.49
135	0.49
146	2.84

Assay 8

[4672] In Vivo Pharmacokinetics in Rodents (e.g. Mice)

[4673] The housing and handling of animals was performed in strict compliance with the European and German Guidelines for Laboratory Animal Welfare. Animals received food and water ad libitum. For the quantification of circulating compounds in plasma, a certain dose (1-100 mg/kg) was orally administered to female NMRInu/nu mice at the age of 6-8 weeks in a solubilized form (n=3 mice per time point).

[4674] Blood was collected into Lithium-Heparin tubes (Monovetten@, Sarstedt) and centrifuged for 15 min at 3000 rpm. A small aliquot (e.g. 100 μL) from the supernatant (plasma) was taken and precipitated by addition of an aliquot ice cold acetonitrile (e.g. of 400 μL) and frozen at −20° C. over night. Samples were subsequently thawed and centrifuged at 3000 rpm, 4° C. for 20 minutes. Aliquots of the supernatants were taken for analytical testing using an Agilent HPLC-system with LCMS/MS detection. PK parameters were calculated by non-compartmental analysis using a PK calculation software.

Assay 9

Validation of PDE3A Modulator-Induced PDE3A Protein Interactions Using Immunoprecipitation and Immunoblotting

[4675] HeLa cells were transfected with ORF overexpression constructs expressing V5-tagged SLFN12, or V5-tagged GFP. ORF expression constructs were obtained from the TRC (clone IDs: TRCN0000468231, TRCN0000476272, ccsbBroad304_99997). At 72 hours post transfection, cells were treated with 10 μM DNMDP or trequinsin for 4 hours followed by lysis using the ModRipa lysis buffer and immunoprecipitation of PDE3A. For each condition, 2 mg total protein lysate was incubated with 1 μg of anti-PDE3A antibody at 4° C. overnight, after which 7.5 μl each of Protein A- and Protein G-Dynabeads (Life Technologies 10001D and 10003D) were added and incubated for another 1 hour. Beads were washed and bound proteins were eluted with 30 μl of LDS PAGE gel loading buffer. Input (~60 μg total protein lysate) and IP products were resolved on 4-12% Tris-Glycine PAGE gels and immunoblotted with an anti-V5 antibody (Life Technologies R96205, 1:5000), the Bethyl anti-PDE3A antibody (1:1000), and secondary antibodies from LiCOR Biosciences (Cat. #926-32210 and 926068021, each at 1:10,000). Blots were washed and imaged using a LiCOR Odyssey infrared imager.

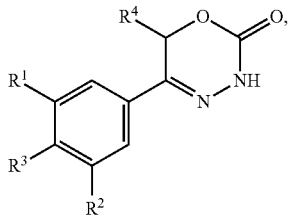
OTHER EMBODIMENTS

[4676] From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein to adopt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

[4677] The recitation of a listing of elements in any definition of a variable herein includes definitions of that variable as any single element or combination (or subcombination) of listed elements. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

1. A compound of formula (I)

formula (I)



where

R^1 is selected from a hydrogen atom, a halogen atom, a cyano group, a C_1-C_3-alkyl group, a C_1-C_3-haloalkyl group, and a C_1-C_3-haloalkoxy group;

R^2 is selected from a hydrogen atom and a halogen atom;

R^3 is selected from,

- a C_1-C_6-alkyl group which is optionally substituted with one or two substituents and each substituent is independently selected from a hydroxy group, a C_1-C_4-alkoxy group and a 3- to 7-membered heterocycloalkyl group;
- a C_2-C_6-alkenyl group which is optionally substituted with an C_1-C_4-alkoxy group;
- a C_3-C_9-cycloalkyl group, which is optionally substituted with a hydroxy group;
- a C_5-C_9-cycloalkenyl group, which is optionally substituted with a hydroxy group;
- a 3- to 9-membered heterocycloalkyl group, comprising one, two or three heteroatoms which are independently selected from —O—, —S—, —S(O)—, $S(O)_2$, and —NR^9—,
  - and said heterocycloalkyl group optionally further comprising a bridging group selected from —O—, —NR^9—, —CH_2—, —CH_2—CH_2—, —O—CH_2—, —CH_2—O—, —NR^9—CH_2—, and —CH_2—NR^9—;
  - and said heterocycloalkyl group is optionally substituted with one, two or three substituents and each substituent is independently selected from
  - a halogen atom;
  - a oxo(=O) group;
  - a cyano group;
  - a hydroxy group;